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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,842	11/17/2000	Roger Briesewitz	STAN-131	8224

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/716,842	**Applicant(s)** BRIESEWITZ ET AL.	
	Examiner Phuong Huynh	**Art Unit** 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 February 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *None*.
   Claim(s) objected to: *None*.
   Claim(s) rejected: *16-18,22-26,30-34,36, 40-44, 46-50 and 52-56*.
   Claim(s) withdrawn from consideration: *None*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection of claims 24 and 26 under 35 U.S.C. 102(b) as being anticipated by Forsgren et al (Cancer Res 39(12): 5155-64, Dec 1979; PTO 892) as evident by Asai et al (Acta Endocrinol (Copenh) 87(1): 173-80, Jan 1978; PTO 892) is hereby withdrawn in view of the amendment to claim 24.

The rejection of claims 16-18, 22-26, 30-34, and 36 under 35 U.S.C. 102(b) as being anticipated by Szepeshazi et al (Anticancer Drugs 8(10): 974-87, November 1997; PTO 892) as evident by Nagy et al (Proc Natl Acad Sci USA 93: 2464-2469, March 1996; PTO 892) and Nagy et al (Proc Natl Acad Sci USA 93: 7269-7273, July, 1996: PTO 892) is hereby withdrawn in view of the amendment to claims 16 and 24.

The rejection of claims 24-25 under 35 U.S.C. 103(a) as being unpatentable over Forsgren et al (Cancer Res 39(12): 5155-64, Dec 1979; PTO 892) as evident by Asai et al (Acta Endocrinol (Copenh) 87(1): 173-80, Jan 1978; PTO 892) in view of Trouet et al (Proc Natl Acad Sci USA 79: 626-629, Jan 1982; PTO 892) is hereby withdrawn in view of the amendment to claim 24.

Continuation of 11. does NOT place the application in condition for allowance because: The following rejections remain.

Claims 16-18, 22-26, 30-34, and 36 stand rejected under 35 U.S.C. 112, first paragraph for enablement. This is because the amended claims 16 and 24 still recite the targeting moiety is any "peptidyl-prolyl isomerase ligand" for the claimed method. The specification discloses only three peptidyl-prolyl isomerase ligands and they are: FK506, rapamycin and cyclosporin. Said ligands are linked to a drug for a method of directing the drug to an intracellular space upon administration to a mammalian host. Other than the specfic peptidyl-prolyl isomerase ligands conjugated to a drug for the claimed method, there is insufficient guidance as how to make other peptidyl-dyl-prolyl isomerase bifunctional molecule having a molecular weight that does not exceed about 5000 daltons for the claimed method.

Claims 16-18, 22-23, 30-34, 36, 40-44, 46-50 and 52-56 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Forsgren et al (Cancer Res 39(12): 5155-64, Dec 1979; PTO 892) in view of WO 95/02684 (Jan 1995; PTO 1449).

Applicants' arguments filed 2/21/06 have been fully considered but are not found to be persuasive.
Applicants' position is that the WO95/02684 does not teach a moiety such as peptidyl-prolyl isomerase ligand FK506 type ligand, cyclosporine, and rampamycin as a targeting domain of a chimeric molecule but instead teaches that such molecules can be targeted, thereby inducing oligomerization in the cell. FKBP12 is a peptidyl-prolyl isomerase, not the ligand for a peptidyl-prolyl isomerase. The disclsoure of FK506, cycloporine and rampamycin in WO95/02684 is within the context of their use as oligomerizing ligands, not as targeting domains of bifunctional molecules. The combined teachings of WO 95/02684 with that of Forsgren et al would be a bifunctional molecule having a drug moiety and a targeting moiety that is peptidyl-prolyl isomerase, not a bifunctional molecule having a drug moiety and a targeting moiety that is a ligand of a peptidyl-prolyl isomerase.

In response, the WO 95/02684 teaches peptidyl-prolyl isomerase ligand such as FK506 and cyclosporin that binds to intracellular biodistribution modulating protein such as FKBP12 to form complex such as FKBP12-FK506 complex (see page 35, lines 19-36, page 40, lines 25-40, in particular). The use of the binding partner of FKBP or cyclophilin, in this case, the ligand FK506 and cyclosporine, respectively, as a targeting moiety to target drug is an obvious variation of the reference teachings, especially in light of the teachings of the WO95/02684 that FK506 interacts with FKBP12 while cyclosporine A interacts with its intracellular receptor cyclophilin (page 40 lines 25-29) and the ligand has a size limitation of less than 5 kD (see page 4, line 13, page 33, lines 22-26, in particular). In fact, the WO95/02684 publication also teaches FK506 (targeting moiety) capable of binding to receptor domain, i.e. FKBP (see page 35, line 24, in particular) linked to a drug moiety such as cyclosporine A (see page 77, line 15, in particular).

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